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(71) Applicant *(for all designated States except US):* NOVEN PHARMACEUTICALS, INC. [US/US]; 13300 S.W. 128th Street, Miami, FL 33186 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only) :* MANTELLE, Juan, A. [US/US]; 10821 S.W. 92nd Avenue, Miami, FL 33176 (US).

(74) Agent: MELOY, Sybil; Foley & Lardner, Suite 403, 501 Brickell Key Drive, Miami, FL 33131 (US).

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(57) Abstract

A composition for topical application comprising a therapeutically effective amount of a pharmaceutical agent(s), a flexible, finite, pharmaceutically acceptable, adhesive, and a solvent for the pharmaceutical agent(s) in the adhesive and a method of administering the pharmaceutical agent to a mammal are disclosed.

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COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent Application Serial Number 07/661,827 filed February 27, 1991, and U.S. Serial Number 07/813,196 filed December 23, 1991, both of which applications are hereby incorporated by reference.

Field of the Invention

The present invention relates to compositions and methods for the topical administration of pharmaceutically active agents, namely those having a pharmacological or cosmetic effect, to a mammal in need thereof. The present invention is especially useful with local anesthetic agents for topical administration. In addition, the invention relates to a method for the topical administration of a pharmaceutical agent, especially an anesthetic agent or a combination of anesthetic agents, to prevent or ameliorate a disease or other medical or cosmetic condition, especially pain.

There is no limitation on the type of pharmaceutical agent that can be used in the present invention, provided that the agent can be absorbed percutaneously. Thus, the pharmaceutical agents can be drugs that can be topically applied for local effects and those which can be topically applied for systemic effects.

Background of the Invention

Anesthetic agents are pharmacologically active agents that block nerve conduction when applied in therapeutically effective amounts. They can be used for local or systemic effects. Anesthetic agents

have been used extensively in the medical field to obtain topical anesthesia. Topical administration or application means the direct contact of the anesthetic with tissue to be anesthetized, such as skin or membrane, particularly the oral or buccal mucosa. Previous methods of applying topical anesthetic agents to the skin or mucosa have used "nonfinite" or semi-liquid carriers or spreading substances such as creams, gels or ointments, or "finite" carriers, non-spreading substances which retain their form, e.g. patches, dressings and bandages. The finite carriers are flexible in the sense that they can bend to conform to the configuration of the skin or mucosa where they are applied.

Local anesthetics generally are esters or amides of benzoic acid derivatives, administered either as the free base or the acid-addition salt. Free bases tend to be irritating at high concentrations. Acid-addition salts have low skin permeability.

To be effective, a topical, local anesthetic should contain sufficient concentration of the active agent to produce an anesthetic effect, it should penetrate intact skin or mucosa sufficiently to deliver a therapeutic dose, and it should exhibit rapid onset of anesthetic action and have a prolonged anesthetic effect. In achieving the foregoing, it is often desirable to have the anesthetic agent present in a high concentration in the dosage form to effect a rapid onset and, additionally or alternatively, in excess of the amount that can be immediately absorbed through the dermis at the site of application, so as to prolong the duration or effect of anesthesia. On the other hand, the presence of the anesthetic agent in crystalline form may irritate sensitive tissues such as mucosal tissues. This is particularly true

with regard to lidocaine. The usefulness of topical anesthetics has been limited by the concentration of drug achievable in the dosage form. The same considerations also apply generally to other pharmaceutically active agents.

Anesthetic agents have been used in nonfinite form. United States Patent No. 4,894,232 to Reüll, et al. discloses a base for mucosal or denture adhesive pastes and a process for the preparation thereof. A lidocaine salt is named as suitable for this paste.

Finite local anesthetic compositions are reported in the literature. Some compositions are solvent free. For instance, Swedish Patent Publication No. 352,239 published December 27, 1972 in the name of S.G. Davis et al., assigned to Astra Pharmaceutical Products, Inc., and based on Swedish patent application No. 17744/70 filed December 30, 1970, discloses a local anesthetic film containing up to 50% lidocaine in crystallized, microdispersed form. In its final form, this composition lacks a solvent for the anesthetic agent. The preparation is prepared by adding a solution of lidocaine in an organic solvent or an acid addition salt in water, under heat and agitation, to a solution or suspension of a film-forming material, namely carboxymethyl cellulose, polyvinyl alcohol, or a mixture of polyvinyl alcohol and polyvinyl pyrrolidone in water, followed by heating to remove any solvent present.

United States Patent No. 4,900,552 of Sanvordeker et al., disclose a trilaminate film suitable for prolonged and sustained delivery of an active ingredient in a buccal cavity. Specifically a hydratable mucoadhesive base layer, a non-adhesive reservoir layer containing the drug and a water-impermeable carrier film sandwiched between and bonded

to the base layer and the reservoir layer form the trilaminate film.

Some finite anesthetic compositions contain polyhydric alcohol solvents. United States Patent Nos. 4,572,832 and 4,695,465 to Kigasawa and 3,249,109 to Maeth all describe the use of water soluble protein based systems which incorporate anesthetics, and which also contain a tackifier and a polyhydric alcohol.

Some finite anesthetic agent compositions have a separate adhesive. United States Patent No. 3,814,095 to Lubens describes an absorbent pad for topical application of an anesthetic agent having a peripheral adhesive.

Glycerol (glycerin) has been used as a plasticizer for karaya gum. United States Patent Nos. 4,307,717 and 4,675,009 to Hymes et. al., describe a drug in a solid phase formed of a synthetic polymer and/or a long chain natural or synthetic polysaccharide or a combination thereof and a liquid phase of water or an alcohol or a combination thereof. The amount of drug in the preparation (excluding solvent or carrier) is low. The cross-linked polysaccharide plasticized with water and/or a polyhydric alcohol is said to be not self-adhering. The formulations do not include both a solvent for the drug and a plasticizer for the polysaccharide.

It is also known to combine two local anesthetic free bases with different melting points. By mixing the two anesthetic bases, an eutectic mixture has been reported that is liquid at room temperature, making it possible to attain higher concentrations of the active bases. United States Patent No. 4,888,354 to Chang relates to a combination of the free base and an acid addition salt or a variety of drugs, typically in a liquid carrier, to increase skin penetration rates. Anesthetics, along

with a list of other suitable drugs are mentioned. This reference specifically teaches that base and acid-addition forms of the same drug be used in carrier.

United States Patent No. 2,352,691 to Curtis teaches the use of salicylate salts of alkamine esters of aminobenzoic acid to enhance the water solubility of anesthetic agents. In one example, this reference discloses a solution of procaine acetyl salicylate containing insoluble anesthetics such as benzocaine, butesin, orthoform, or their salts, in certain glycols, which are combined with a volatile solvent, and then used to saturate gauze bandages or other suitable fabrics.

United States Patent No. 2,142,537 to Tisza describes an ointment containing isoamylhydrocupreine in combination with a quick acting local anesthetic to overcome the undesirable irritation caused by the prolonged acting anesthetic isoamylhydrocupreine or its salts. The preparation of Tisza combines short and long acting anesthetic agents.

United States Patent No. 2,277,038 to Curtis relates to preparations containing a mixture of two or more anesthetic agent salts having different pH values in solution, whereby the pH value of the combined mixture in solution may be adjusted to obtain a higher degree of stability of the solution, and at relatively higher pH, a more rapid onset of anesthetic action. The anesthetic agents in Curtis are not in highly dispersed form and are used in a liquid-soaked fabric.

Commonly, prolongation of anesthesia with topical anesthetics has been achieved by the addition of vasoconstrictors, such as the catecholamine, epinephrine, which caused constriction of blood vessels. Since catecolamines are not particularly effective when applied topically, such a prolongation

is of minimal usefulness for topical anesthetics. The primary drawbacks of this approach are the potential adverse side effects of catecolamines, and the prolongation itself.

Although many local anesthetic compositions have been proposed, it has been discovered that the incorporation of one or more anesthetic agents in a solvent for the anesthetic agent or agents into a flexible, finite, pharmaceutically acceptable carrier, permits an exceptionally high loading of anesthetic agent in the carrier, permitting more rapid delivery of the anesthetic agent to the dermal membrane and a greater extent of anesthesia without crystallization of the anesthetic agent or agents which can limit absorption by the skin and which can cause irritation of the skin or other dermal membrane.

It has also surprisingly been found that concentrations of substantially dissolved anesthetic agent as high as 50% by weight of the total composition can be achieved in a system in which the adhesion of the adhesive is not hindered. Prolongation of anesthesia can thus be achieved by increasing the amount of time the composition is applied, without detrimental irritation.

The compositions of the present invention are in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate the dermis, for example, intact skin or a mucous membrane. Moreover, the anesthetic action is highly localized. Because the drug is substantially microdispersed in the carrier, it is more readily available for permeation into the skin or dermal membrane.

It still further has surprisingly been found that the use of two different local anesthetic agents, the first in base form and the second in acid-addition

salt form, in a finite, flexible, adhesive, pharmaceutically acceptable carrier, including a solvent for the anesthetic agents, permits the attainment of anesthetic agent concentrations in the final product of up to 50% by weight in microdispersed form, without crystallization of the anesthetic agents which can cause irritation of the skin or other dermal membrane.

Thus, in one embodiment, the present invention is in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate intact skin or mucous membranes and have a highly localized effect. Furthermore, the combination of the salt and base forms, advantageously results in rapid onset of anesthetic action with prolonged anesthetic effect.

Summary of the Invention

The invention relates to a flexible, finite bioadhesive composition, for topical application comprising:

a therapeutically effective amount of at least one local anesthetic or other pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the anesthetic or other pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent based on the weight of the whole composition of a plasticizer for the bioadhesive;

in admixture with the anesthetic agent or other pharmaceutically active agent in the solvent, a flexible, finite, pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20

to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention is comprised of two anesthetic agents, that is:

a therapeutically effective amount of a first local anesthetic agent in base form;

a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form;

a solvent for the first and second local anesthetic agents, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition; and

in an admixture with the anesthetic agents and the solvent, a pharmaceutically acceptable adhesive, preferably a bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the anesthetic agents preferably are in non-crystallized form in the composition.

The compositions of the invention may be further include a backing material which conforms to the size and shape of a single dosage of the composition.

The present invention further relates to a method of administering one or more pharmaceutically active agents in a bioadhesive to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures; a pharmaceutically acceptable solvent for the pharmaceutically active agent, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive; and in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is substantially free of water, is substantially water insoluble and is self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

The invention further relates to a method of administering two local anesthetic agents to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of a first local anesthetic agent in base form; a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form; a pharmaceutically acceptable solvent for the anesthetic preferably in an amount which ranges from about 50 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive carrier; and in admixture with the

pharmaceutically active agent in the solvent, a pharmaceutically acceptable preferably polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition thereby administering the local anesthetic agent.

The compositions of this invention permit a far higher loading of drug than conventional dosage forms. This loading in the case of anesthetic agents can result in an extent (depth) of anesthesia which numbs the teeth when applied buccally, not a typical result for a topical anesthetic cream or ointment.

Detailed Description of the Invention

This invention provides a composition which adheres to an area of the skin or mucosa, and permits delivery at elevated levels of pharmaceutical agent or a combination of agents to produce a local or systemic effect over a prolonged period of time.

In accordance with one embodiment of the present invention, a local anesthetic in solution with a solvent for the anesthetic, containing a plasticizer for the adhesive, is in admixture with a pharmaceutically acceptable adhesive, which is preferably a bioadhesive, and more preferably a polysaccharide bioadhesive, is provided in a finite, flexible form for topical application to the skin or dermal membrane of a mammal.

In accordance with a further embodiment of the present invention, a combination of local anesthetic agents, a solvent for the anesthetic agents

and a flexible, preferably adhesive pharmaceutically acceptable adhesive carrier is provided for topical application to the skin or mucosa of a mammal.

The anesthetic agents of this invention are those known, or of a type known, in the art. The local anesthetic bases encompassed by this invention are weak organic bases which are lipophilic in nature and thus poorly soluble in water. However, these bases will react with organic or inorganic acids to form acidic, water soluble acid-addition salts.

The base form and the salt form of the anesthetic agent incorporated in the combination composition of this invention must be different anesthetic agents, to achieve maximum duration of the anesthetic effect. By the term "different" is meant that the salt form in any combination is not a salt of the base form used in the given combination.

Local anesthetic agents suitable for use in the practice of this invention include amides and esters. Examples of the amides are lidocaine, prilocaine, mepivacaine, bupivacaine, dibucaine and etidocaine. Esters include procaine, tetracaine, propoxycaine, chloroprocaine, benzocaine, butamben picrate, cocaine, hexylcaine, piperocaine, oxyprocaine and proparacaine. Other suitable local anesthetics for use in the practice of this invention include cyclomethycaine, dimethisoquin, ketocaine, diperodon, dyclonine and pramoxine, all typically administered in the form of the acid addition hydro-chloride or sulfate salts.

The acid-addition salts of the present invention are any non-toxic, pharmaceutically acceptable organic or inorganic salts. Typical inorganic salts are the hydrogen halides, especially the hydrochlorides, carbonates, borates, phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates,

sulfides, and arsenates. Typical organic salts are salts of mono- and polycarboxylic acids such as the citrate, tartrate, malate, cinnamate, oxalate, formate, succinate and phthalates.

The solvents for the anesthetic agents or other drugs are non-toxic, pharmaceutically acceptable substances, preferably liquids, which do not substantially negatively affect the adhesion properties of the system and in which the anesthetic agents or other drugs in the amounts employed are fully soluble. Preferably, the solvent is or is primarily a polyhydric alcohol or combination of polyhydric alcohols, particularly when the adhesive is a gum. The term polyhydric alcohol means any organic polyol. Other suitable solvents include carboxlyic acids and their derivatives and analogs such as fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols and ketones such as polyvinylpyrrolidone. Further suitable solvents include other non-toxic, non-volatile solvents commonly used in dermal or transdermal compositions for dissolving like compounds. As apparent to one skilled in the art what is a suitable solvent varies with the solubility of the drug in question.

The above mentioned polyhydric alcohols may include those having 2 to 6 alcoholic hydroxyl groups. Such polyhydric alcohols include glycols, triols and polyols having 4 to 6 alcoholic hydroxyl groups. Typical of said glycols are glycols containing 2 to 6 carbon atoms, e.g. ethylene glycol, propylene glycol, butylene glycol, polyethylene glycol (average molecular weight about 200 - 8,000, preferably about 200 to 6,000), dipropylene glycol, hexylene glycol, polyoxyethylene, polypropylene glycol, sorbitol, and the like. Examples of said triols include glycerin,

trimethylolpropane. Said polyols are exemplified by cycloalkanepolyols such as polyols derived from monosaccharides such as sorbitol (sorbit). These polyhydric alcohols may be used either singly or in combination (preferably, of two or three). Thus, for example, glycerin alone or a mixture of glycerin and butylene glycol is employed. In general, when an anesthetic agent, especially an anesthetic base is used, there are limits to the amounts of lipophilic polyhydric alcohols containing more than two alcoholic hydroxyl groups that can be present in the solvent and yet not result in precipitation of the drug as crystals.

Among those polyhydric alcohols, those which satisfy the requirements relevant to the adjustment and maintenance of softness of the external drug of the invention, the compatibility or co-dispersibility with the other components, and provide a proper consistency of the composition, may be freely used. Those which are low in volatility and plastic, are generally preferred and, in this regard, dipropylene glycol, glycerin, propylene glycol, butylene glycol, and sorbitol are appropriate solvents, according to the invention. Since solvent is to remain, at least in part, in the composition, the solvent should include components that do not substantially volatilize under the drying conditions used in preparing the composition. In other words, the solvent for the drug should be non-volatile.

Solvent selection for a single anesthetic agent or a combination of anesthetic agents in either the free base form or in the acid-addition salt form, depends on the form of the anesthetic agent, namely whether it is in free base form or acid-addition salt form. Solvents for the salt form of anesthetic agent are polar organic solvents. Polar organic solvents

are preferably polyhydric alcohols, as discussed above. Various other solvents suitable for either the base or acid-addition form of the anesthetic agent are those solvents known to dissolve either or both of these two types of forms including cyclic ketones such as 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted alkyl-azacycloalkyl-2-ones (azones) dimethylformadide, and dimethylsulfoxide.

Other suitable solvents for the free base form of the anesthetic agent are cell envelope disordering compounds known to be useful in topical pharmaceutical preparation, which compounds are thought to assist in skin penetration by disordering the lipid structure of the stratum corneum cell-envelopes. Some of these compounds are generally encompassed by the formula:

R-X

wherein R is a straight-chain alkyl of about 7 to 16 carbon atoms, a non-terminal alkenyl of about 7 to 22 carbon atoms, or a branched-chain alkyl of from about 13 to 22 carbon atoms, and X is -OH, -$COOCH_3$, -$COOC_2H_5$, -$OCOCH_3$, -$SOCH_3$, -$P(CH_3)_2O$, -$COOCH_2H_4OC_2H_4OH$, -$COOCH(CHOH)_4CH_2OH$, -$COOCH_2CHOHCH3$, -$COOCH_2CH(OR")CH_2OR"$. -$(OCH_2CH_2)_mOH$, -COOR', or -$CONR'_2$ where R; is -H, -CH_3, -C_2H_5, -C_3H_7 OR -C_2H_4OH; R" is -H, or a non-terminal alkenyl of about 7 to 22 carbon atoms; and m is a positive integer from 2 to 6; provided that when R" is an alkenyl and X is -OH or -COOH, at least one double bond is in the cis-configuration.

Although the exact amount of the polyhydric alcohol or alcohols in the composition depends on the nature of other components, and therefore cannot be stated in specific terms, the proportion may range

from about 5 to about 70 weight percent based on the whole composition.

The solvent includes from about 5% to about 50% and more preferably about 10% to about 30% of a polyhydric alcohol known to plasticize the bioadhesive carrier. A particularly useful plasticizer is glycerine.

The high concentrations of microdispersed drug, for example anesthetic agent, of this invention are achieved typically by mixing the anesthetic agents with the solvent, preferably at an elevated temperature, for example about 70° to 100°C, to obtain a mixture, preferably a solution, of the anesthetic agents which is then added to the pharmaceutically acceptable adhesive.

Preferably the anesthetic agent is substantially dissolved in the solvent so that when mixed with the adhesive, the anesthetic is microdispersed in the composition. The term "microdispersed" is intended to mean that in the solvent, and subsequently in the carrier, there is an intimate dispersion of the anesthetic agent at the molecular or ionic level, such that crystals of the anesthetic agent cannot be detected using a microscope having a magnification of roughly 25X. As such, the pharmaceutically active agent is in "non-crystallized" form when in the compositions of the present invention.

It has been discovered that high concentrations of a combination of microdispersed anesthetic agents, namely up to 50% by weight of the finite, flexible composition, require the use of a solvent as herein described. Omission of the solvent in the procedure of Example 1 below yields a product filled with crystals or crystalline mass.

In particularly preferred embodiments of this invention, the free base local anesthetic agent is selected from the group comprising lidocaine, procaine, propoxycaine, mepivacaine, prilocaine, dyclonine, pramoxine, benzocaine and chloroprocaine. The salt form is preferably one selected from the group comprising prilocaine, tetracaine, bupivacaine, dyclonine, dibucaine, etidocaine and lidocaine salts. The aforementioned bases and salts can be used alone or in combination with other anesthetic bases and salts as needed to achieve therapeutically affective levels when administered transdermally.

The term "therapeutically effective amount" is intended to mean the amount of drug as a minimizer sufficient to produce a therapeutic effect, for example, an anesthetic effect when applied topically. These amounts are known in the art or may be determined by methods known in the art, and typically range from about 1 to 20,000 mg per human adult and preferably about 10 to 10,000 mg and most preferably range from about 20 to 5,000 mg of the anesthetic agent per application, depending upon the anesthetic agents chosen, and whether the skin or mucous membrane is the site of action. The only upper limit on the amount of anesthetic in the composition is that the preparation is substantially free of crystals of anesthetic agent or other drug and the amount of solvent used is not sufficient to undesirably affect the adhesive properties of the whole composition. Thus, the single ingredient anesthetic agent contains as a minimizer a therapeutically effective amount of anesthetic agent within the foregoing range.

The concentration as well as the quantity of anesthetic per square centimeter can be varied independently in order to achieve the desired effect. Higher concentrations of anesthetic base contained in

a dosage form of decreased thickness will result in a anesthetic with fast onset and short duration. High concentrations of the anesthetic base contained in a dosage form of increased thickness (higher mg of anesthetic per square centimeter) will result in potent anesthesia with fast onset and long duration. Low concentrations of the anesthetic base in a dosage form of decreased thickness will result in mild anesthesia with longer onset and short duration. Low concentrations of the anesthetic base contained in a dosage form of increased thickness will have mild anesthesia with longer onset and longer duration. As shown in the above explanation, the ability to vary the concentration of anesthetic from very low (about 1%) to high (40% or higher) of the total composition, when combined with the ability to coat thin (about 0.001 inches) or thick (about 0.500 or more inches) enables the practitioner of the invention to vary the dosage of the system as needed for particular anatomical sites of interest.

As a general rule, in the case of mucosal application, the anesthetic drug selected, the concentration and thickness and the duration of the application is determined based upon the anesthetic's ability to penetrate the mucosa and to be at peak effectiveness within about 2 to 30 minutes. The duration of the effect of the anesthetic on the oral mucosa should range between about 2 to 240 minutes, depending on the anesthetic agent selected, the concentration of the anesthetic and the thickness of application. Longer or shorter durations can also be selected dependent on need, as will be apparent to one skilled in the art.

The ratio of the free base form to the salt form in the alternate composition of this invention will depend on several factors, namely: (1) the

identity of the salt and base used; (2) the desired duration of action; and (3) the desired rapidity of anesthetic effect. As a general rule in the case of mucosal application, the ratios of base to salt are such that the free base form preferably should penetrate the mucosa and be at its peak effectiveness within about a 2 to 30 minute period, whereas, the salt form should preferably penetrate the mucosa and be at its peak effectiveness within a period of about 10 to 75 minutes. The duration of the effect of these on the oral mucosa will range between about 2 to 240 minutes depending on the base/salt combination selected and the length of application time.

The term "onset of anesthesia" is intended to mean the time to peak effect on the individual nerves. Onset of anesthesia principally depends upon the lipid solubility, molecular size, and quantity of available, un-ionized form of the local anesthetic. Thus, anesthetics with a high lipid solubility or a low pK_a, or both, have a more rapid onset of anesthesia.

The term "duration of anesthesia" as used herein means the period of time during which the local anesthetic measurably blocks nerve conduction. The foregoing depends upon all of the factors listed for onset of anesthesia, as well as on the extent of protein binding of the anesthetic agent.

The anesthetic agent free base can penetrate intact skin to a limited degree, and will more rapidly penetrate the skin if the keratin layers are abraded. In the case of the oral mucosa, the anesthetic base will penetrate much more readily due to the different keratin composition and the resulting difference in the hydrophilicity as compared to the stratum corneum of intact skin.

As a general rule, the salt forms of the aforementioned anesthetics do not appreciably penetrate intact skin, but the un-ionized base form do penetrate to a limited degree. Both forms, salt and base, will penetrate abraded keratin layers. The salt as well as the base will penetrate, to a differing degree, the buccal mucosa due to the buccal mucosa's hydrophilicity, as compared to the stratum corneum of intact skin. Generally, the higher the lipid content of the mucosal membrane, the more rapidly the base form of the anesthetic agent will be absorbed. Therefore, when the composition is used for application to oral or buccal mucosa, the different lipid contents of the gum (gingiva) and the alveolar mucosa must be kept in mind in order to obtain the optimal penetration rate.

Although applicants do not intend to be bound by any theory or proposed mechanism of operation, it is believed that the base which is lipid soluble has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction. On the other hand, the salt which is not lipid soluble, penetrates to the lipo-protein nerve membrane only after the buffering capacity of the skin or mucosal tissue converts the salt to the base, the final result being a delayed onset of anesthesia.

The salts of this invention in the combination composition are selected on the basis of onset of anesthesia and duration of anesthesia. Adjusting the ratio of base to salt affects the relative onset as well as the duration of anesthetic action. The greater the amount of anesthetic agent having a rapid onset of action, the shorter the onset of anesthesia. Similarly, the greater the amount of the anesthetic agent having a prolonged duration of

anesthesia, the more prolonged the duration of anesthesia. More than two anesthetic agents may be used to have a broader spectrum of activity. Moreover, the composition can include other drugs used concomitantly.

Generally, the concentration of solubilized anesthetic agent can range, on a weight basis, between about 1 and about 50% or more, preferably between 2.5 and 40% and more preferably between 5 and 30% of the total weight of the composition. In a preferred embodiment of the combination of this invention, the concentration of dissolved base is 20% by weight of the total composition. The base used in the preferred embodiment for a single ingredient preparation is lidocaine.

Generally, for the hydrochloride salts the ratio by weight of base to salt is about 90:10 to about 60:40, preferably about 75:25 to about 60:40, and more preferably about 70:30 to about 60:40. For other salts, the ratios are comparable based on relative molar amounts. In a preferred embodiment of the invention, the ratio is about 2:1 base to salt, respectively. The base used in the preferred embodiment is lidocaine and the preferred salt is a salt of prilocaine, bupivacaine, dyclonine, mepivacaine, or tetracaine, preferably the hydrochloride salt.

Table 1 below summarizes the peak and duration of action of selected local anesthetics based primarily on application to skin or mucous membranes:

TABLE 1

Local Anesthetic	Minimum Adult Dose	Maximum Adult Dose (mg)	Peak Effect (minutes)	Duration of Effect (minutes)
Dibucaine		25	< 15	120-240
Lidocaine		750	2-5	30-60
Benzocaine		5000	1	30-60
Cocaine		50	2-5	30-120
Tetracaine		50	3-8	30-60
Dyclonine		100	< 10	< 60
Pramoxine		200	3-5	NA

NA: Not Available.

Source: Drug Facts and Comparisons, 1990 edition, J.B. Lippincott Company, St. Louis, MO. Page 601.

In general, the relative speed of onset of anesthesia and duration of anesthesia for any given form of anesthetic agent is available in the literature or can be calculated by standard tests.

Onset time, as well as duration of anesthesia, will vary from individual to individual as well as on the basis of the site of application. When applying the composition to highly keratinized dermal tissues, the onset of anesthesia may take as long as 2 to 4 hours.

The composition of this invention can be manufactured by numerous methods known in the art which permit the achievement of a microdispersed anesthetic agent, including extruding, molding, solvent casting, coating, and all other methods which employ a solvent to disperse the drug in a carrier prior to shaping of the carrier.

Contrary to the typical method for manufacturing a drug in a solvent containing adhesive, the preparation is either not dried so as to force removal of the solvent from the adhesive or a solvent

is used which is not substantially evaporated during the conditions of manufacture. The composition in question can then be applied to a flexible backing or a combination of backings which will serve to define the size and shape of a single dosage of the composition. Such backing may be a three dimensional material such as paper, a non-woven fabric or natural or synthetic polymer substance. Methods of coating backings are well-known in the art and include techniques involving Mayer rod, gravure, and knife-over roll. Further processing of backings may involve the use of converting equipment for die cutting.

The finished dosage form will be substantially occlusive to water permeation in in-vivo.

For example, the anesthetic agents are dissolved in a solvent, preferably a polyhydric alcohol, and then the resulting mixture is added to an adhesive prior to being placed onto the flexible form or backing. The final form in which the composition of the invention will be applied depends upon the anatomical site of application.

The phrase "flexible, finite" with reference to the pharmaceutically acceptable carrier, is intended to mean a solid capable of conforming to a surface with which it comes into contact and capable of maintaining the contact so as to facilitate topical application without any adverse physiological response, and which can be used to establish the compositions herein in their preferred solid form without being appreciably decomposed by aqueous contact during administration to a patient.

An important characteristic of the present invention relates to the substantially water-free and water-insoluble nature of the composition. By the term "substantially water-free" is meant that the

preparation contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3%. In general, it is desirable to avoid the addition of water entirely and to eliminate, as far as possible, the presence of water in the other ingredients of the composition. By the term "substantially water insoluble" is meant that the composition remains "finite" and does not generally detach from the skin or other dermal membrane at the site of application and under the conditions of regular, intended use for a period of at least 3 hours. The advantages to be derived from the substantially water-free and water-insoluble nature of the compositions of the present invention include achievement of higher concentrations of drug. Another advantage of these compositions is minimization of precipitation of drug into crystals, which precipitation affects processing of the composition, affects rate of delivery of the drugs and in certain cases can affect sensitivity of the subject to be treated to the drug.

Suitable adhesive carriers include any of the non-toxic polymers, particularly those of the type used to carry drugs for transdermal delivery including natural or synthetic elastomers, such as polyisobutylene, styrene, butadiene, styrene isoprene block copolymers, acrylics, urethanes, silicones, styrene butadiene copolymers, methyl acrylate copolymers, acrylic acid, polyacrylates, and polysacchrides such as, karaya gum, tragacanth gum, pectin, guar gum, cellulose, and cellulose derivatives such as methyl cellulose, propyl cellulose, cellulose acetate and the like, along with other substances known for use in transdermal preparations capable of forming a solid colloid that can adhere to skin and mucosa, used alone or in

combination with other suitable carriers. A particularly preferred carrier is a bioadhesive and more preferably a polysaccharide bioadhesive for application to the dermis, preferably the mucosa. The adhesive can be modified so as to adhere to the skin or mucosal tissue, depending on the intended application site.

The term "adhesive" as used herein means a substance, inorganic or organic, natural or synthetic, that is capable of surface attachment to the intended application site.

The term "bioadhesive" as used herein means an adhesive which attaches and preferably strongly attaches to a live or freshly killed biological surface such as skin or mucosal tissue upon hydration. Indeed, to qualify as a bioadhesive, a substance must be capable of maintaining adhesion in moist or wet in *in-vivo* or *in-vitro* environments. The final composition of the present invention is "self-adhesive" in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive which is applied to the composition.

The strength of adherence can be measured by standard tests for measuring the force, e.g. in dynes per square centimeter, as disclosed in U.S. 4,615,697. Suitable bioadhesives include those prepared from optionally partially esterified or etherified polyacrylic acid polymers, including but not limited to, polyacrylic acid polymers lightly cross-linked with a polyalkenyl polyether or other cross-linking agent such as those commercially available from B.F. Goodrich, Cincinnati, Ohio, under the trademarks Carbopol 934, 934P, 940 and 941.

Other suitable bioadhesives include natural or synthetic polysaccharides. The term "polysaccharide" as used herein means a carbohydrate

decomposable by hydrolysis into two or more molecules of natural or synthetic monosaccharides or their analogs or derivatives. Suitable polysaccharides include cellulose derivatives such as methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like. Other suitable bioadhesives are pectin, a mixture of sulfated sucrose and aluminum hydroxide, hydrophilic polysaccharide gums such as natural plant exudates, including karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like, as well as seed gums such as guar gum, locust bean gum, psillium seed gum and the like.

In addition to the above ingredients, there may also be incorporated other additives selected from among the various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, penetration enhancers, flavorings and pigments. In the preferred embodiment, the compositions of the present invention also contain a binder or emulsifier such as lecithin which promotes dispersion of the other ingredients having differing solubilities, thereby enhancing the uniform consistency of the final composition.

The composition is administered in appropriate sizes, typically having a surface area of from about 0.1 to about 200 cm^2 or conveniently 0.2 to 100 cm^2. The anesthetic agent is loaded into the composition in as high a concentration as necessary to effect therapy, e.g., in a range from about 0.1 mg/cm^2 to about 50 or more mg/cm^2.

In general, the composition can have the following types and amounts of ingredients:

Ingredient	Typical Range (% by weight)	Preferred Range (% by weight)	Optimum Range (% by weight)
Adhesive	15 to 60	20 to 50	20 to 35
Solvent	2 to 75	5 to 70	20 to 40
(plasticizer included in solvent)	1 to 50	5 to 50	10 to 30
Anesthetic agent (single ingredient)	1 to 50	5 to 40	10 to 30
Anesthetic agent (multiple ingredient)	1 to 50	5 to 40	10 to 30
(a) Anesthetic base	.7 to 50	5 to 40	7 to 20
(b) Anesthetic salt	.3 to 25	2 to 30	3 to 20

In one embodiment, the flexible, finite, bioadhesive composition for topical application comprises:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active

agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention comprises;

a composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a pharmaceutically acceptable, adhesive-containing carrier containing a solvent for the first and second local anesthetic agents.

wherein the composition is preferably substantially free of water, and substantially water insoluble and is self-adhesive; and wherein the anesthetic agents are in non-crystallized form in the composition.

Preferably, the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive carrier is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition. More preferably, the composition is comprised of 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and is further comprised of a binder in or emulsifier an amount sufficient to bind the other ingredients.

Another embodiment of the invention relates to a method of administering one or more local anesthetics to a subject in need of such local anesthetic. The term "administering" is intended to mean any mode of application which results in the physical contact of the composition with an anatomical

site in need of anesthesia. The term "subject" is intended to include all warm-blooded mammals, including humans.

The following examples will further describe the instant invention, and are used for the purposes of illustration only, and should not be considered as limiting in any way the invention being disclosed herein. Percent (%) as used in these examples refer to percentage of the liquid formulation on a weight to weight basis and temperatures are given in degrees celsius (°C).

Example 1

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (prilocaine hydrochloride)	14

The final product is manufactured by first blending the lidocaine base, prilocaine hydrochloride, propylene glycol, lecithin and glycerin at about 70 to 90°C until all of the drug is dissolved. The solution is then cooled to 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven, polyester film (for example, the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

Example 2

Ingredient	% (w/w)
Adhesive (karaya gum)	30
Solvent/plasticizer (glycerin)	30
Solvent (propylene glycol)	39
Anesthetic agent base (lidocaine base)	0.7
Anesthetic agent salt (prilocaine hydrochloride)	0.3

The procedure set forth in Example 1 is used with appropriate substitutions of quantities to prepare this formulation.

Example 3

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	4
Solvent (propylene glycol)	3
Solvent (isocetyl alcohol)	7
Solvent/plasticizer (glycerin)	26
Anesthetic agent base (lidocaine base)	26
Anesthetic agent salt (tetracaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 4

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Solvent (propylene glycol)	29
Solvent/plasticizer (glycerin)	4
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (dyclonine hydrochloride)	12

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 5

Ingredient	% (w/w)
Adhesive (karaya gum)	26
Binder (lecithin)	10
Solvent (propylene glycol)	7
Solvent (butylene glycol)	17
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (lidocaine base)	20
Anesthetic agent salt (dyclonine hydrochloride)	10

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 6

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	27
Anesthetic agent salt (bupivacaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 7

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	13
Anesthetic agent salt (bupivacaine hydrochloride)	27

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 8

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (mepivacaine hydrochloride)	14

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 9

Ingredient	% (w/w)
Adhesive (Carbopol 934P, a polycarboxylic acid sold by B.F. Goodrich Chemical Company)	20
Solvent (propylene glycol)	15
Solvent/plasticizer (glycerin)	20
Anesthetic agent base (lidocaine base)	30
Anesthetic agent salt (bupivacaine hydrochloride)	15

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 10

Ingredient	% (w/w)
Adhesive (karaya gum)	24
Solvent (propylene glycol)	3
Solvent/plasticizer (glycerin)	14
Solvent (isocetyl alcohol)	7
Binder (lecithin)	4
Anesthetic agent base (lidocaine base)	32
Anesthetic agent salt (tetracaine hydrochloride)	16

The above formulation is prepared by a procedure which is analogous to that set forth in Example 1.

The addition of up to 2% by weight water in this formulation did not result in precipitation of the anesthetic agent(s) prior to addition of the karaya gum. The addition of 3% to 10% water results in increased precipitation, which at 10% water results in a crystalline mass.

Example 11

Ingredient	% (w/w)
Adhesive (tragacanth gum)	24
Adhesive (pectin)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	12
Anesthetic agent base (mepivacaine base)	35
Anesthetic agent salt (lidocaine hydrochloride)	12

The above formulation is prepared by a procedure analogous to that of Example 1.

Example 12

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The final product is manufactured by first blending the lidocaine base, lecithin, propylene glycol, dipropylene glycol and glycerine at about 70 to 90°C until all of the drug is dissolved. The solution is then chilled to about 20 to 40°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven polyester film (for example the film sold under the trademark Sontata 8100 manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed at about 70 to 130°C to accelerate the formation of the gel into its final

solid form. This gel can be directly applied to the oral mucosa or overlaid with a skin contact adhesive for skin adhesion.

Example 13

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	33
Anesthetic agent base (lidocaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 14

Ingredient	% (w/w)
Bioadhesive (karaya gum)	35
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	36
Anesthetic agent base (lidocaine base)	5

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 15

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 16

Ingredient	% (w/w)
Bioadhesive (karaya gum)	20
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	10
Solvent (benzyl alcohol)	5
Anesthetic agent base (lidocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 17

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	8
Solvent (isocetyl alcohol)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (prilocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 18

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	4
Solvent (propylene glycol)	6
Solvent (benzyl alcohol)	10
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	5
Anesthetic agent base (tetracaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 19

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	8
Solvent (propylene glycol)	12
Solvent (dipropylene glycol)	25
Solvent (benzyl alcohol)	5
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (dibucaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 20

Ingredient	% (w/w)
Bioadhesive (karaya gum)	28
Bioadhesive (Carbopol 934 Trademark of B.F. Goodrich)	2
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Binder (lecithin)	9
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation. The only difference is that the carbopol 934 is added to the original blend prior to heating it.

Example 21

Ingredient	% (w/w)
Bioadhesive (tragacanth gum)	27
Bioadhesive (pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is used with the solvents and anesthetic agent base added in the initial step followed later by the adhesives addition.

Example 22

Ingredient	% (w/w)
Bioadhesive (cellulose acetate)	27
Solvent (dipropylene glycol)	33
Anesthetic agent base (prilocaine base)	20
Solvent/plasticizer (glycerin)	10

This formulation is prepared according to the procedure which is analogous to the procedure set forth in Example 1.

Example 23

Ingredient	% (w/w)
Bioadhesive (Xanthan gum)	27
Bioadhesive (Pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is followed with the appropriate substitution of ingredients.

Example 24

Ingredient	% (w/w)
Drug (miconazole nitrate)	2
Solvent (propylene glycol)	67
Thickener (hydroxymethylcellulose)	1
Adhesive (karaya gum)	30

This formulation is prepared by dispersing the hydroxymethylcellulose into the propylene glycol. Once the hydroxymethylcellulose is dispersed, the drug is added at a temperature between 50 and 80°C and mixed until dissolved. The sample is then cooled to approximately 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the formulation is applied to a sheet of backing material, then the individual dosage forms are cut to the desirable shape to contain the desired amount of drug.

Example 25

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	32.5
Plasticizer (glycerin)	32.5
Adhesive (karaya gum)	30.0

Example #25 is prepared just as Example #24.

Example 26

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	17.5
Plasticizer (glycerin)	30.0
Solvent (propylene glycol)	7.0
Binder (lecithin)	10.5
Adhesive (karaya gum)	30.0

Example #26 is prepared just as Example #24.

Example 27

Ingredient	% (w/w)
Drug (miconazole base)	10
Solvent (propylene glycol)	35
Plasticizer (glycerin)	25
Adhesive (karaya gum)	30

Example #27 is prepared just as Example #24.

Example 28

Ingredient	% (w/w)
Drug (clotrimazole)	1.0
Solvent (propylene glycol)	41.3
Plasticizer (glycerin)	24.7
Adhesive (karaya gum)	33.0

Example #28 is prepared just as Example #24.

Example 29

Buccal formulations containing, respectively, 5%, 10%, 20%, and 25% lidocaine were prepared according to the procedure of foregoing

examples. A patch containing no drug (placebo patch) was also used.

The patches were tested on nine human subjects. The patch was applied to the buccal cavity of the mouth and removed after 15 minutes. The patch was placed on the gingival surface, since the gingival surface was found to be the best site to examine for a dose response relationship.

The extent of anesthesia at 5, 10, 15, 30, 45, and 60 minutes after application was determined by measurement of the extent of anesthesia. The exent of anesthesia was determined by a base line discomfort tolerance limit determined by application of a tip of a periodontal probe, to the treated surface. The patient was asked to determine the depth penetration they could tolerate at the various timed intervals.

Five minutes after initiation of treatment there was no statistical differences in pain toleration between the treatment groups, including the placebo and no-patch.

At ten minutes post application the 25% lidocaine patch produced the greatest mean change in response threshold followed by the 10 and 20% lidocaine patches. There was little difference between the 5% lidocaine and placebo patch. Lidocaine concentrations greater than 5% were necessary to produce a significant increase in pain threshold responses, and there was a distinct trend in dose proportionality in the range of 10% - 25% lidocaine.

The median change in response thresholds for the gingival surface group displayed the same relationship. The 25% lidocaine patch provided the greatest anesthetic effect followed by the 10% and 20% lidocaine patches.

When all the sites were combined into one group and the median change from baseline was plotted,

the graph revealed a dose response profile where the doses appear in order of concentration from 10 to 30 minutes post application. The 25% lidocaine patch provided the greatest increase in response threshold. The 10% and 20% lidocaine patch responses were similar with the 20% lidocaine patch being slightly better.

There were no signs of inflammation, tissue damage, or other adverse effects associated with application of the patches.

Similar studies were conducted in which the patch was applied to the gingival sulcus and the interproximal sulcus.

Certain of the lidocaine preparations were distinguised in that they resulted in the numbness of the teeth, an effect not generally observed with topical anesthetics applied in fluid vehicles.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modification without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as described in this specification and the appended claims.

Indeed, the present invention is intended to encompass and be suitable for any pharmaceutically active agent, especially any of the following drugs as the pharmaceutically active agent in the composition:

1. Analgesic anti-inflammatory agents such as, acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, l-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, alclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen, protizidic acid, fentiazac, tolmetin,

tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and the like;

2. Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like;

3. Antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like;

4. Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like;

5. Steroids such as, androgenic steriods, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, 17β-estradiol esters such as 17β- estradiol

valerate, equilin, mestranol, estrone, estriol, 17β-estradiol derivatives such as 17β-ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like;

6. Respiratory agents such as, theophylline and β_2-adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, and the like;

7. Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like;

8. Antimicrobial agents including antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides, nitrofrantoin, anti fungals, such as, clotrimazole, miconazole, chloramphenicol, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like;

9. Antihypertensive agents such as, clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like;

10. Antihypertensive diuretics such as, chlorothiazide, hydrochlorothrazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like;

11. Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like;

12. Coronary vasodilators such as, organic nitrates such as, nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like;

13. Vasoconstrictors such as, dihydroergotamine, dihydroergotoxine, and the like;

14. β-blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like;

15. Calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like;

16. Anti-convulsantants such as, nitrazepam, meprobamate, phenytoin, and the like;

17. Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like;

18. Tranquilizers such as, reserprine, chlorpromazine, and antianxiety benzodiazepines such as, alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like;

19. Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranqulizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like;

20. Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine;

21. Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like;

22. Respiratory agents such as, codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like;

23. Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like;

24. Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like for dermatologically use;

25. Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like;

26. Enzymes such as, lysozyme, urokinaze, and the like;

27. Herb medicines or crude extracts such as, glycyrrhiza, aloe, Sikon (Lithospermi radix), and the like;

28. Miotics such as pilocarpine, and the like;

29. Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like;

30. Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like;

31. Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, hydroxyamphetamine, and the like;

32. Psychic energizers such as, 3-(2-aminopropy)indole, 3-(2-aminobutyl)indole, and the like;

33. Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE_1, $PGE_{2\alpha}$, and $PGF_{2\alpha}$, and the PGE_1 analog misoprostol.

34. Antispasmodics such as, atropine, methantheline, papaverine, cinnamedrine, methscopolamine, and the like;

35. Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like;

36. Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like;

37. Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like;

38. Anti-allergenics such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like;

39. Decongestants such as, phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like;

40. Antipyretics such as, aspirin, salicylamide, and the like;

41. Antimigrane agents such as, dihydroergotamine, pizotyline, and the like;

42. Anti-malarials such as, the 4-aminoquinolines, alphaaminoquinolines, chloroquine, pyrimethamine, and the like;

43. Anti-ulcer agents such as, misoprostol, omeprazole, enprostil, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsuflate, and the like;

44. Peptides such as, growth releasing factor, and the like;

45. Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like.

The drugs mentioned above can be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters can be employed.

All the drugs used are in solid form at ambient, namely room, temperatures and pressures. However liquid drugs can also be employed to the extent that such drugs, in the forms and amounts used do not undesirably affect the adhesive properties of the carrier.

The acid mentioned above may be an organic acid, for example, methanesulfonic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, acetic acid,

or ann inorganic acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. The base may be an organic base, for example, ammonia, triethylamine, or an inorganic base, for example, sodium hydroxide or potassium hydroxide. The esters mentioned above may be alkyl esters, aryl esters, aralkyl esters, and the like.

When a drug different than an anesthetic agent is used the solvent selected is one in which the drug is soluble. In generally the polyhydric alcohol can be used as a solvent for a wide variety of drugs. Other useful solvents are those known to solubilize the drugs in question.

CLAIMS

1. A flexible, finite, bioadhesive composition for topical application comprising:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

2. The composition of claim 1, wherein the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition, of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition.

3. The composition of claim 1, wherein the pharmaceutically active agent is at least one local anesthetic in an amount of about 10 to about 40 weight percent based on the weight of the total composition.

4. The composition of claim 1, wherein the pharmaceutically active agent is from a class of drugs selected from the group consisting of analgesic anti-inflammatory drugs, central nervous system drugs, antihistaminic or antiallergic drugs, acitonide anti-inflammatory drugs, androgenic and estrogenic steroids, respiratory drugs, sympathomimetic drugs, antimicrobial drugs, antihypertensive drugs, cardiotonic drugs, coronary vasodilators, vasoconstrictors, beta blocking and antiarrhythemic drugs, calcium antagonistic and other circulatory anticonvulsants, anti-vertigo-tranquilizing drugs, antipsychotic drugs, muscle-reactants drugs, anti-Parkinson drugs, non-steroidal hormones, anti-hormones, vitamins, anti-tumor, enzymes, herb medicines or crude extracts, miotics, cholinergic agonists, antimuscarinic or muscarinic cholinergic blocking drugs, mydriatics, psychic energizers, humoral agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine drugs, antimalarial, antiulcer drugs, peptides, and anti-estrogens.

5. The composition of claim 4, wherein the antimicrobial drugs is an antifungal agent selected from the group consisting of chlotrimazole, miconazale and chloramphenicol

6. The composition of claim 4, in which the pharmaceutically active agent is one or more steroids selected from the group consisting of androgenic steroids, including testosterone; methyltestosterone; fluoxymesterone; estrogenic steroids, including conjugated estrogens, esterified estrogens, estropipate, 17ß-estradiol, 17ß-estradiol esters such as 17ß-estradiol valerate, equilin, mestranol, estrone, estriol; 17ß- estradiol derivatives such as

17β-ethinyl estradiol; diethylstilbestrol, progestational agents, including progesterone and progesterone analogs such as 19-norprogesterone, hydroxyprogesterone caproate, 17α-hydroxyprogesterone, dydrogesterone, medroxyprogesterone acetate; and norethindrone, norethindrone acetate, melengestrol, chlormadinone; ethynodiol diacetate, norethynodrel, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and anti-estrogen or anti-androgenic steroids.

7. The composition of claim 3, wherein the anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, chloroprocaine, tetracaine, bupivacaine, and etidocaine and is in the form of the base or an acid-addition salt or both forms.

8. The composition of claim 7, wherein the acid-addition salt is hydrochloride.

9. The composition of claim 1, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

10. The composition of claim 9, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum, guar gum, cellulose, and cellulose derivatives.

11. The composition of claim 1, wherein the solvent for the anesthetic agent is at least one polyhydric alcohol.

12. The composition of claim 11, wherein the polyhydric alcohol is a polyalkylene glycol.

13. The composition of claim 12, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol,

polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

14. The composition of claim 1, further comprising a backing material conforming to the size and shape of a single dosage of the composition.

15. The composition of claim 1 comprising about 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and further comprising a binder in an amount sufficient to bind the other ingredients.

16. The composition of claim 15 comprising about 30 weight percent of karaya gum, about 6 weight percent propylene glycol, about 15 weight percent of dipropylene glycol, about 15 weight percent of glycerine, about 25 weight percent of lidocaine base and about 9 weight percent of lecithin.

17. The composition of claim 15, comprising about 33 weight percent of karaya gum, about 7 weight percent of propylene glycol, about 12 weight percent of dipropylene glycol, 33 weight percent of glycerin, about 10 weight percent lidocaine base and about 5 weight percent lecithin.

18. The composition of claim 1 wherein the pharmaceutical agent comprises a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, local anesthetic agent in acid-addition salt form.

19. The composition of claim 18, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine

salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

20. The composition of claim 21, wherein the acid-addition salt is the hydrochloride.

21. The composition of claim 20, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

22. The composition of claim 21, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

23. The composition of claim 22, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

24. The composition of claim 23, wherein the polyhydric alcohol is a polyalkylene glycol.

25. The composition of claim 24, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

26. A method of administering one or more pharmaceutically active agent to a subject comprising the steps of:

providing the composition set forth in claim 1; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

27. The method of claim 26, wherein the pharmaceutically active agent is an anesthetic agent selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine, chloroprocaine, tetracaine, bupivacaine, etidocaine, and dibucaine.

28. The method of claim 27, wherein the anesthetic agent is administered in the form of a free base.

29. The method of claim 28, wherein the anesthetic agent is administered in the form of an acid-addition salt.

30. The method of claim 29, wherein the solvent is at least one polyhydric alcohol.

31. The method of claim 30, wherein the polyhydric alcohol is a glycol or cycloalkanepolyol.

32. The method of claim 31, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, sorbitol, and ethylene glycol.

33. The method of administering a pharmaceutically active agent of claim 26, wherein the pharmaceutically active agent is a combination of a therapeutically effective amount of a first local anesthetic agent in base form; and a therapeutically effective amount of a different, second local anesthetic agent in an acid-addition salt form.

34. The method of claim 33, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

35. The method of claim 34, wherein the acid-addition salt is hydrochloride.

36. The method of claim 35, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

37. The method of claim 36, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

38. The method of claim 37, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

39. The method of claim 38, wherein the polyhydric alcohol is a polyalkylene glycol or cycloalkanepolyol.

40. The method of claim 39, wherein the glycol or polyol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, and sorbitol.

41. The composition of claim 1, wherein the pharmaceutically active agent is an anti-microbial agent.

42. The composition of claim 41, in which the anti-microbial agent in an antifungal agent.

43. The composition of claim 42 in which the anti-microbial agent is clotrimazole.

44. The composition of claim 43 in which the anti-microbial agent is miconazole.

45. A composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a flexible, finite, pharmaceutically acceptable adhesive-containing solvent for the first and second local anesthetic agents.

46. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, lidocaine,

prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine, and chloroprocaine.

47. The composition of claim 45, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

48. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

49. The composition of claim 48, wherein the salt is the hydrochloride.

50. The composition of claim 45, wherein the adhesive is a bioadhesive.

51. The composition of claim 50, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

52. The composition of claim 50, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

53. The composition of claim 50, wherein the bioadhesive is karaya gum.

54. A method of delivering local anesthetic agents which comprises the topical administration to a mammal of a composition comprising:

a therapeutically effective amount of a first local anesthetic agent in base form and

a therapeutically effective amount of a different, second local anesthetic agent in salt form in admixture with a flexible, finite, pharmaceutically acceptable, adhesive; and

a solvent in the adhesive for the first and second local anesthetic agents.

55. The method of claim 54, wherein the first local anesthetic agent is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

56. The method of claim 55, wherein the salt is a hydrochloride.

57. The method of claim 54, wherein the adhesive is a bioadhesive.

58. The method of claim 57, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

59. The method of claim 57, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

60. The method of claim 57, wherein the bioadhesive is karaya gum.

61. The method of claim 59, wherein the salt is a hydrochloride.

INTERNATIONAL SEARCH REPORT

International Applicat.... No PCT/US 92/01730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/70 A 61 L 15/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	DD,A, 217989 (ERNST MORITZ ARNDT UNIVERSITÄT GREIFSWALD) 30 January 1985, see the whole document ---	9
A	EP,A,0250187 (JOHNSON & JOHNSON PRODUCTS INC.) 23 December 1987, see page 3, line 1 - page 4, line 41; pages 7-9, examples 2-4; pages 11,12, examples 6,7 ---	1-61
A	EP,A,0363224 (BLOCK DRUG CO. INC.) 11 April 1990, see pages 7,8, examples 1,2 ---	1-61
A	WO,A,8910740 (INNOVATA BIOMED LTD) 16 November 1989 --- -/-	1-61

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-07-1992	31. 08. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	LU,A, 52460 (ASTRA PHARMACEUTICAL PRODUCTS) 25 June 1968, see the whole document, in particular page 5, lines 17-23; page 18, example 7	1-61

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/01730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: please see remark
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-40 and 54-61 are directed to a method of treatment of the human/animal the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201730 SA 58216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/08/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DD-A- 217989		None	
EP-A- 0250187	23-12-87	US-A- 4713243	15-12-87
		AU-A- 7415587	17-12-87
		JP-A- 63019152	26-01-88
		US-E- RE33093	17-10-89
EP-A- 0363224	11-04-90	AU-A- 4265689	12-04-90
		CA-A- 2000277	07-04-90
		JP-A- 2196717	03-08-90
WO-A- 8910740	16-11-89	None	
LU-A- 52460	25-06-68	BE-A- 690383	29-05-67
		DE-A- 1617282	06-02-75
		FR-M- 6733	24-02-69
		GB-A- 1108837	
		NL-A- 6616878	31-05-67